

WHAT IS CLAIMED IS:

1. A process for preparing a 3'-O-amino acid ester nucleoside, comprising:
 - (a) coupling an optionally protected, optionally substituted, ribofuranose with an unprotected nucleoside base and a silylating reagent in the presence of a Lewis acid to form an optionally protected nucleoside;
 - (b) optionally reacting the protected nucleoside from step (a) with a deprotecting reagent to provide an unprotected nucleoside if necessary;
 - (c) optionally reacting the amine group of the protected or unprotected nucleoside if the nucleoside has an amine group, with an amine-protecting reagent;
 - (d) optionally reacting the protected or unprotected nucleoside with a silylating reagent to provide a 5'-O-silyl-protected nucleoside;
 - (e) reacting the protected or unprotected nucleoside with a protected amino acid derivative optionally with one or more coupling reagents to form a protected 3'-O-amino acid ester;
 - (f) optionally refluxing the product from step (e) with a reagent that removes the silyl protecting group from the 5'-C and the formamidinium-protecting group from the nucleosidic amine if needed; and
 - (g) optionally reacting the product from step (f) with a reagent that removes the protecting group from the 3'-O-amino acid ester, thereby producing a substituted or unsubstituted 3'-O-ester-substituted nucleoside.
2. The process of claim 1, wherein in step (a), the optionally protected ribofuranose contains a methyl group at the 2'-C position.
3. The process of claim 1, wherein in step (a) the Lewis acid is selected from the group consisting of SnCl₄, BF₃, AlCl₃, TiCl₄, FeCl₃ and SnCl₂.
4. The process of claim 3 wherein the Lewis acid is SnCl₄.
5. The process of claim 1, wherein in step (a), the silylating agent is selected from the group consisting of BSA, HMDS, TMSCl, and TBDPSCl.
6. The process of claim 5 wherein the silylating agent is BSA.
7. The process of claim 1, wherein in step (a), wherein the coupling reaction is achieved in a solvent that is acetonitrile.

8. The process of claim 1, wherein in step (b), the deprotecting agent is NaOMe or NH₃.
9. The process of claim 1, wherein in step (c) the amine-protecting agent is selected from the group consisting of N,N-dimethylformamide dimethyl acetal and N-1,1-dimethylthiomethyleneamine.
10. The process of claim 9 wherein the amine-protecting agent is N,N-dimethylformamide dimethyl acetal.
11. The process of claim 1, wherein in step (d) the silylating reagent is selected from the group consisting of TBDPSCI, TMSCl, and TBDMSCl.
12. The process of claim 11 wherein the silylating reagent is TBDPSCI.
13. The process of claim 1, wherein in step (e) the amino acid derivative is valinyl.
14. The process of claim 1, wherein in step (e) the amino acid protective group is selected from BOC, -(C=O)-aralkyl, -(C=O)-alkyl or -(C=O)-aryl.
15. The process of claim 14 wherein the amino acid protective group is BOC.
16. The process of claim 1, wherein in step (e) one of the coupling reagents is EDC.
17. The process of claim 1, wherein in step (f), the silyl-removing reagent is NH₄F.
18. The process of claim 1, wherein in step (g), the 3'-O-amino acid ester protecting group removing reagent is HCl.
19. A process for preparing a nucleoside comprising the steps of:
 - (a) coupling 1,2,3,5-tetra-O-benzoyl-2-C-methyl-β-D-ribofuranose with cytosine in the presence of BSA and SnCl₄ to form 4-amino-1-(3,4-dibenzoyloxymethyl-5-benzyloxymethyl-3-methyl-tetrahydrofuran-2-yl)-1H-pyrimidin-2-one;
 - (b) reacting the 4-amino-1-(3,4-dibenzoyloxymethyl-5-benzyloxymethyl-3-methyl-tetrahydrofuran-2-yl)-1H-pyrimidin-2-one from step (a) with sodium methoxide to remove the benzoyl protecting groups, thereby providing 4-amino-1-(3,4-dihydroxy-5-hydroxymethyl-3-methyl-tetrahydro-furan-2-yl)-1H-pyrimidin-2-one;
 - (c) reacting the 4-amino-1-(3,4-dihydroxy-5-hydroxymethyl-3-methyl-tetrahydrofuran-2-yl)-1H-pyrimidin-2-one from step (b) with N,N-dimethylformamide dimethyl acetal to protect the N⁴-amino group, thereby producing N-[1-(3,4-dihydroxy-5-hydroxymethyl-3-methyl-tetrahydrofuran-2-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-N,N-dimethyl formamidine;

- (d) reacting the nucleoside from either of steps b) or c) with the silylating reagent TBDPSCI to provide *N'*-{1-[5-(*tert*-butyl-diphenyl-silanyloxymethyl)-3,4-dihydroxy-3-methyl-tetrahydrofuran-2-yl]-2-oxo-1,2-dihydro-pyrimidin-4-yl}-*N,N*-dimethyl-formamidine;
 - (e) reacting the *N'*-{1-[5-(*tert*-butyl-diphenyl-silanyloxymethyl)-3,4-dihydroxy-3-methyl-tetrahydrofuran-2-yl]-2-oxo-1,2-dihydro-pyrimidin-4-yl}-*N,N*-dimethyl-formamidine with *N*-BOC-L-valine and EDC in dichloromethane to provide 2-*tert*-butoxycarbonylamino-3-methyl-butyric acid 2-(*tert*-butyl-diphenyl-silanyloxymethyl)-5-[4-(dimethylamino-methyleneamino)-2-oxo-2*H*-pyrimidin-1-yl]-4-hydroxy-4-methyl-tetrahydrofuran-3-yl ester;
 - (f) removing the silyl-protecting group and the formamidine group from 2-*tert*-butoxycarbonylamino-3-methyl-butyric acid 2-(*tert*-butyl-diphenyl-silanyloxymethyl)-5-[4-(dimethylamino-methyleneamino)-2-oxo-2*H*-pyrimidin-1-yl]-4-hydroxy-4-methyl-tetrahydrofuran-3-yl ester in step (e) by refluxing the compound with NH₄F to form 2-*tert*-butoxy-carbonylamino-3-methyl-butyric acid 5-(4-amino-2-oxo-2*H*-pyrimidin-1-yl)-4-hydroxy-2-hydroxymethyl-4-methyl-tetrahydrofuran-3-yl ester; and
 - (g) removing the BOC-protecting group from the 3'-O-valinyl-ester substituent by reacting the 2-*tert*-Butoxycarbonylamino-3-methyl-butyric acid 5-(4-amino-2-oxo-2*H*-pyrimidin-1-yl)-4-hydroxy-2-hydroxymethyl-4-methyl-tetrahydro-furan-3-yl ester from step (f) with HCl to provide 2-amino-3-methyl-butyric acid 5-(4-amino-2-oxo-2*H*-pyrimidine-1-yl)-4-hydroxy-2-hydroxymethyl-4-methyl-tetrahydro-furan-3-yl ester (dihydro-chloride salt).
20. A process for preparing a furanose comprising:
- (a) reacting aqueous CaO with a cyclic ether that contains a hydroxyl and a CH₂OH on the carbon adjacent to the ring oxygen, thereby forming a furanyl lactone;
 - (b) optionally protecting the furanyl lactone with a protecting group if necessary;
 - (c) reacting the optionally protected furanyl lactone with a reducing agent to reduce the lactone to a hydroxyl group, creating a furanose product compound; and
 - (d) optionally reacting the furanose product compound with a protecting group.

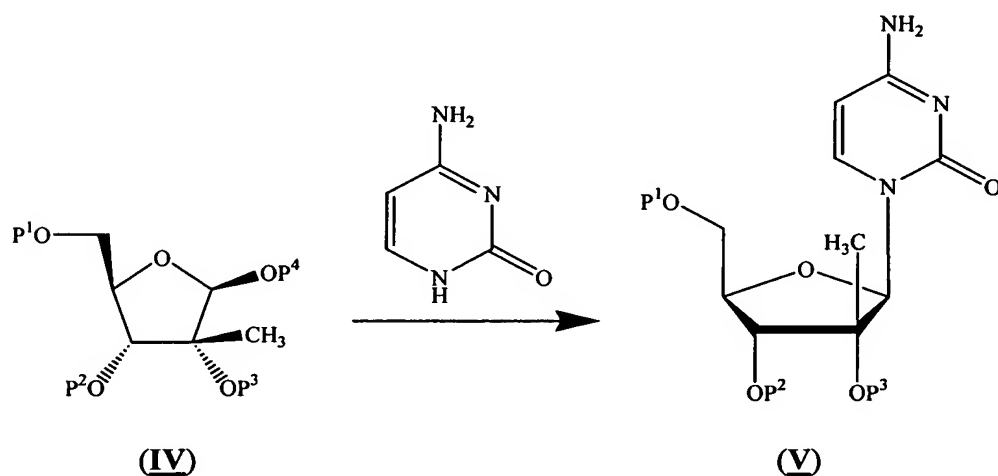
21. The process of claim 20 wherein the cyclic ether reacted with CaO is D-fructose.
22. The process of claim 20 wherein the furanyl lactone is 2-C-methyl-D-ribono-lactone.
23. The process of claim 20 wherein the protected furanyl lactone is 2,3,5-tri-O-benzoyl-2-C-methyl-D-ribono-lactone.
24. The process of claim 20 wherein the furanose is 2,3,5-tri-O-benzoyl-2-C-methyl- β -D-ribofuranose.
25. The process of claim 20 wherein the protected furanose is 1,2,3,5-tetra-O-benzoyl-2-C-methyl- β -D-ribofuranose.
26. The process of claim 20 wherein the protecting group is selected from the group consisting of silyl, benzoyl, p-toluoyl, p-nitrobenzoyl, p-chlorobenzoyl, acyl, acetyl, -(C=O)-alkyl, and -(C=O)-aryl, optionally substituted with one or more groups not affected by the reducing agent of step (c).
27. The process of claim 26 wherein the protecting group is benzoyl.
28. The process of claim 26 wherein the protecting group is -(C=O)-alkyl.
29. The process of claim 20 wherein the reducing agent is selected from the group consisting of Red-Al/ethanol, NaHTe, SmI₂, H₂ + Pd-phosphine catalyst, and LiAl(O^tBu)₃H.
30. The process of claim 29 wherein the reducing agent is Red-Al/ethanol.
31. The process of claim 20 wherein the reactions are carried out in solvent selected from the group consisting of TEA, DMAP, DME, toluene and ethanol.
32. The process of claim 20 wherein the reaction temperature varies from about -5 °C to about 50 °C for the first product compound lactone.
33. The process of claim 20 wherein the total time for synthesis is from about 5 days to about 14 days.
34. The process of claim 33 wherein the total time for synthesis is from about 5 days to 10 days.
35. The process of claim 33 wherein the total time for synthesis is about 60 hours.
36. A process comprising:
 - (a) reacting aqueous CaO with D-fructose for about 5 hours to about 25 hours at a temperature from about 23 °C to about 40 °C;
 - (b) reacting the product from step (a) with CO₂ and oxalic acid for about 8 hours to about 12 hours, to form 2-C-methyl-D-ribonolactone;

- (c) reacting 2-C-methyl-D-ribonolactone with benzoyl chloride for about 3 hours to about 6 hours to provide 2,3,5-tri-O-benzoyl-2-C-methyl-D-ribonolactone;
 - (d) reducing 2,3,5-tri-O-benzoyl-2-C-methyl-D-ribonolactone with Red-Al/ethanol for about 30 to about 60 minutes at a temperature of from about – 5 °C to about 0 °C to afford 2,3,5-tri-O-benzoyl-2-C-methyl-β-D-ribofuranose;
 - (e) benzoylating 2,3,5-tri-O-benzoyl-2-C-methyl-β-D-ribofuranose in solvent for about 4 hours to about 14 hours at a temperature of from about 0 °C to about 50 °C to form 1,2,3,5-tetra-O-benzoyl-2-C-methyl-β-D-ribofuranose; and
 - (f) optionally isolating the 1,2,3,5-tetra-O-benzoyl-2-C-methyl-β-D-ribofuranose.
37. The process of claim 36, step (a), wherein the reaction time is from about 6 to about 22 hours.
 38. The process of claim 36, step (a), wherein the temperature is from about 23 to about 40 °C.
 39. The process of claim 36, step (c), wherein the solvent is DME.
 40. The process of claim 36, step (c), wherein the reaction proceeds for about 4 hours.
 41. The process of claim 36, step (d), wherein reduction proceeds for about 40 minutes.
 42. The process of claim 36, step (d), wherein the solvent comprises toluene.
 43. The process of claim 36, step (e), wherein the solvent comprises DME.
 44. The process of claim 36, step (e), wherein the temperature is from about 5 to about 50 °C, and the reaction runs for from about 4 to about 12 hours.
 45. The process of claim 36, step (f), wherein isolation is performed by methods known in the art.
 46. The process of claim 1 wherein the benzoyl-protected, optionally substituted ribofuranose is prepared by the process of claim 20.
 47. The process of claim 1 wherein the benzoyl-protected, optionally substituted, ribofuranose is prepared by the process of claim 36.

48. A process for preparing a furanyl lactone comprising: <
(a) reacting aqueous CaO with a cyclic ether that contains a hydroxyl and a CH₂OH on the carbon adjacent to the ring oxygen, thereby forming a furanyl lactone. 6
49. A process for preparing a 2-C-methyl-D-ribonolactone, the process comprising:
(a) reacting aqueous CaO with D-fructose for about 5 hours to about 25 hours at a temperature from about 23 °C to about 40 °C;
(b) reacting the product from step (a) with CO₂ and oxalic acid for about 8 hours to about 12 hours, to form 2-C-methyl-D-ribonolactone. 1
50. A process for preparing an optionally protected 2-C-methyl-β-D-ribofuranose compound comprising:
(a) reducing an optionally protected 2-C-methyl-D-ribonolactone with Red-Al/ethanol to obtain an optionally protected 2-C-methyl-β-D-ribofuranose.
51. A process for preparing an optionally protected nucleoside, comprising: 2
(a) coupling an optionally protected, optionally substituted, ribofuranose with an unprotected nucleoside base and a silylating reagent in the presence of a Lewis acid to form an optionally protected nucleoside.
52. A process for preparing an optionally protected β-D-2'-C-methyl-cytidine 9
comprising the steps of:
(a) coupling an optionally protected 2-C-methyl-β-D-ribofuranose with cytosine in the presence of BSA and SnCl₄, to form an optionally protected β-D-2'-C-methyl-cytidine.

53. A process for preparing a 2'-C-methyl-cytidine comprising the steps of:

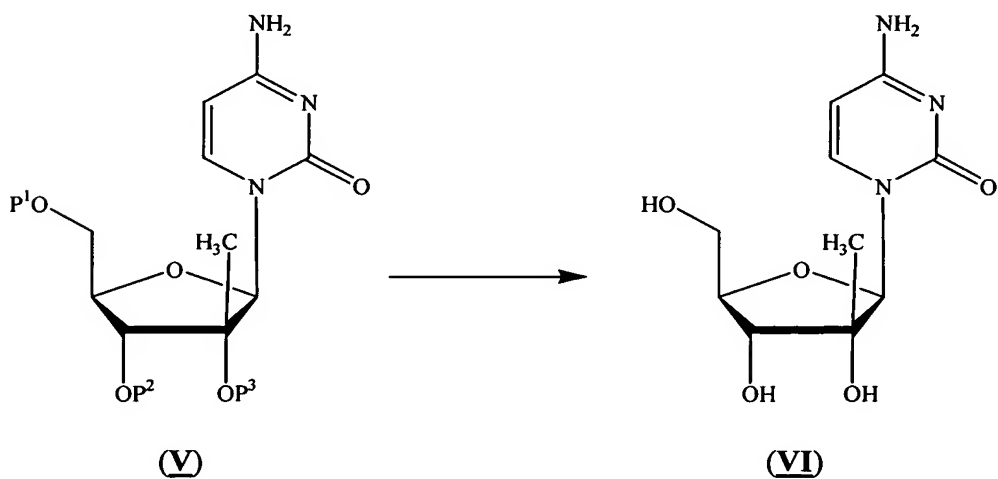
- (a) reacting cytosine and an activator, optionally in the presence of a Lewis acid, with an optionally protected 2-C-methyl- β -D-ribofuranose to form an optionally protected 2'-C-methyl-cytidine



wherein each P^1 , P^2 , P^3 , and P^4 is independently hydrogen or a suitable oxygen protecting group;

and then

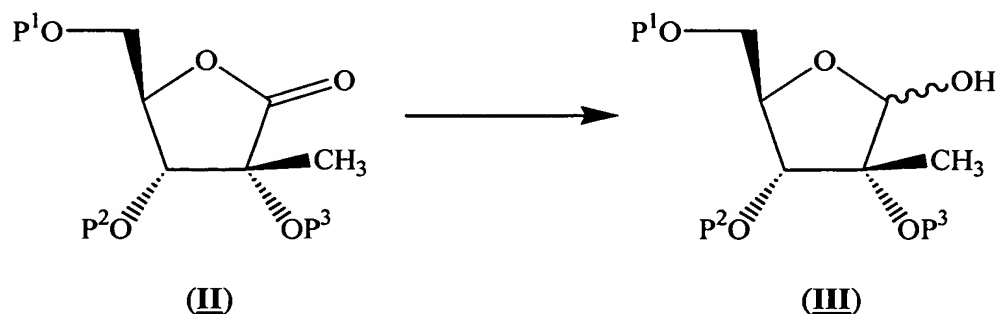
- (b) optionally deprotecting the optionally protected 2'-C-methyl-cytidine of the previous step to form 2'-C-methyl-cytidine (VI)



if necessary.

54. The process of claim 53, wherein, each P^1 , P^2 , P^3 , and P^4 is independently hydrogen or an acyl.
55. The process of claim 53, wherein, each P^1 , P^2 , P^3 , and P^4 is independently hydrogen or a benzoyl.
56. The process of claim 53, wherein the activator is a silylating agent.
57. The process of claim 56, wherein the silylating agent is BSA, HMDS, TMSCl, or TBDPSCl.
58. The process of claim 56, wherein the silylating agent is BSA.
59. The process of claim 53, wherein the reaction of step (a) is accomplished with a Lewis acid selected from the group consisting of SnCl_4 , BF_3 , AlCl_3 , TiCl_2 , TiCl_4 , FeCl_3 , SnCl_2 , and any mixture thereof.
60. The process of claim 53, wherein the Lewis acid is SnCl_4 .
61. The process of claim 53, wherein the process further comprises the steps of esterifying the 3'-position of the 2'-C-methyl-cytidine with an ester moiety.
62. The process of claim 61, wherein the ester moiety is an amino acid.
63. The process of claim 62, wherein the amino acid is L-valinyl.
64. A process for preparing an optionally protected 2-C-methyl- β -D-ribofuranose comprising the steps of:

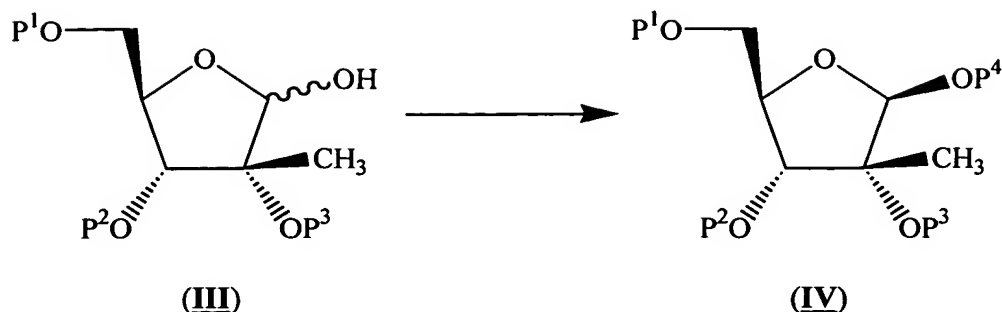
- (a) reducing an optionally protected 2-C-methyl-D-ribonic lactone with a reducing agent



wherein each P^1 , P^2 , and P^3 is independently hydrogen or a suitable oxygen protecting group;

and then

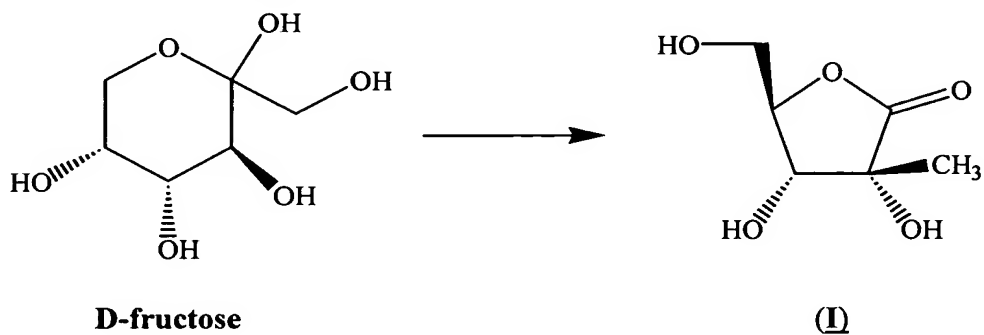
- (b) optionally protecting the ribofuranose derivative compound of the previous step to form an optionally protected 2-C-methyl- β -D-ribofuranose



wherein P⁴ is independently hydrogen or a suitable oxygen protecting group.

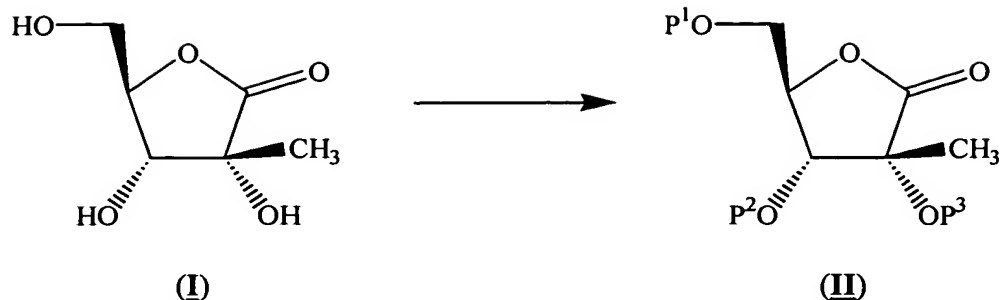
65. The process of claim 64, wherein, each P¹, P², P³, and P⁴ is independently hydrogen or an acyl.
66. The process of claim 64, wherein, each P¹, P², P³, and P⁴ is independently hydrogen or a benzoyl.
67. The process of claim 64, wherein the reducing agent is sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), optionally in a solvent.
68. The process of claim 67, wherein the solvent is ethanol.
69. A process for preparing an optionally protected 2-C-methyl-D-ribonic lactone comprising the steps of:

(a) reacting D-fructose with CaO;



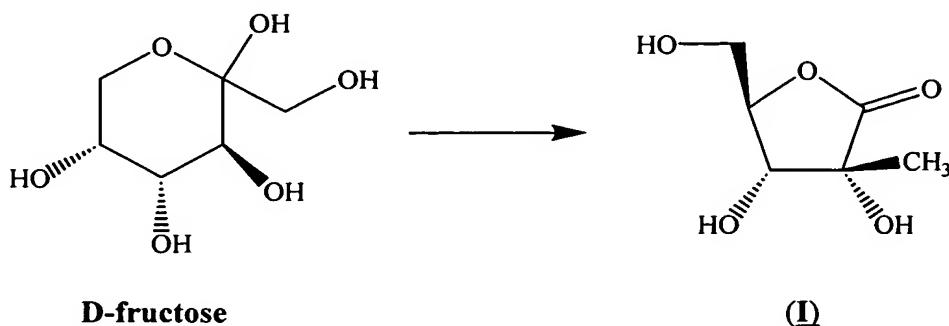
and then,

- (b) optionally protecting the lactone, to form an optionally protected 2-C-methyl-D-ribonic lactone

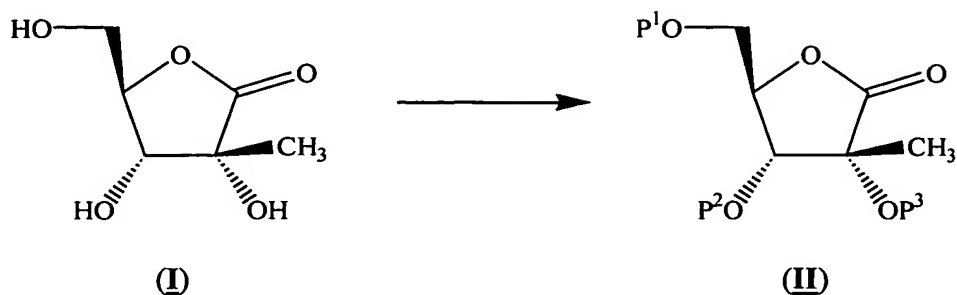


wherein each P^1 , P^2 , and P^3 is independently hydrogen or a suitable oxygen protecting group.

70. The process of claim 69, wherein, each P^1 , P^2 , and P^3 is independently hydrogen or an acyl.
71. The process of claim 69, wherein, each P^1 , P^2 , and P^3 is independently hydrogen or a benzoyl.
72. The process of claim 69, wherein a precipitant is used to remove calcium generated in step (a).
73. The process of claim 72, wherein the precipitant is an organic acid that is stronger than ribonic acid.
74. The process of claim 73, wherein the organic acid is selected from the group consisting of oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, suberic acid, sebacic acid, azelaic acid, maleic acid, acetic acid, propionic acid, isobutyric acid, acrylic acid, methacrylic acid, butyric acid, pentanoic acid, hexanoic acid and hexanoic acid.
75. The process of claim 73, wherein the organic acid is oxalic acid.
76. A process for preparing an optionally protected 2'-C-methyl-D-cytidine from D- γ -fructose, comprising the steps of:
 - (a) reacting D-fructose with CaO to obtain a 2-C-methyl-D-ribonic- γ -lactone;

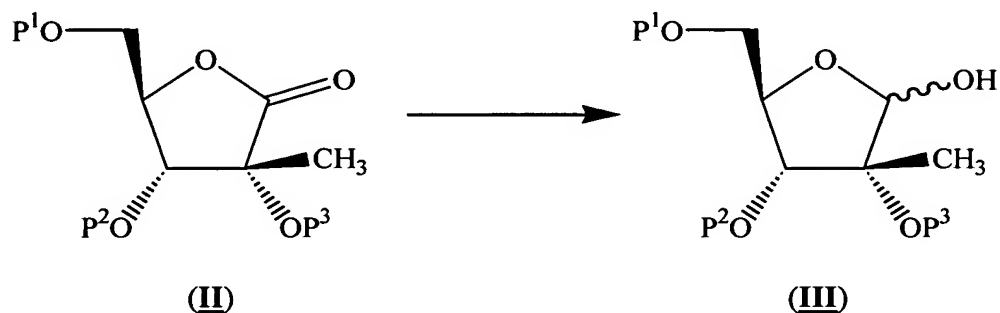


- (b) optionally protecting the lactone to form an optionally protected 2-C-methyl-D-ribonic lactone, if necessary;



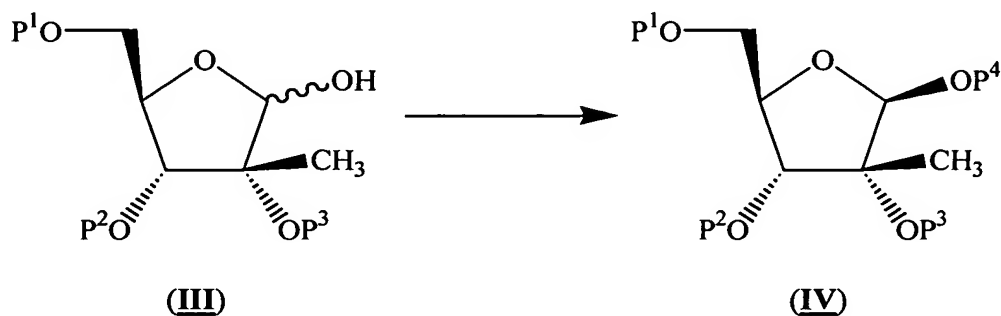
wherein each P^1 , P^2 , and P^3 is independently hydrogen or a suitable oxygen protecting group;

- (c) reacting the optionally protected 2-C-methyl-D-ribonic lactone with a reducing agent;



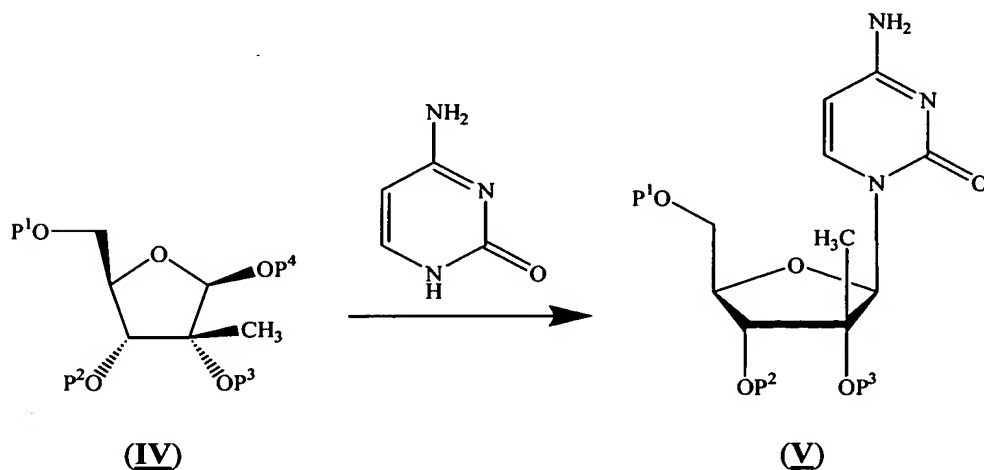
wherein each P^1 , P^2 , and P^3 is independently hydrogen or a suitable oxygen protecting group;

- (d) optionally protecting the ribofuranose derivative compound of the previous step to form an optionally protected 2-C-methyl- β -D-ribofuranose if necessary,



wherein P^4 is independently hydrogen or a suitable oxygen protecting group;

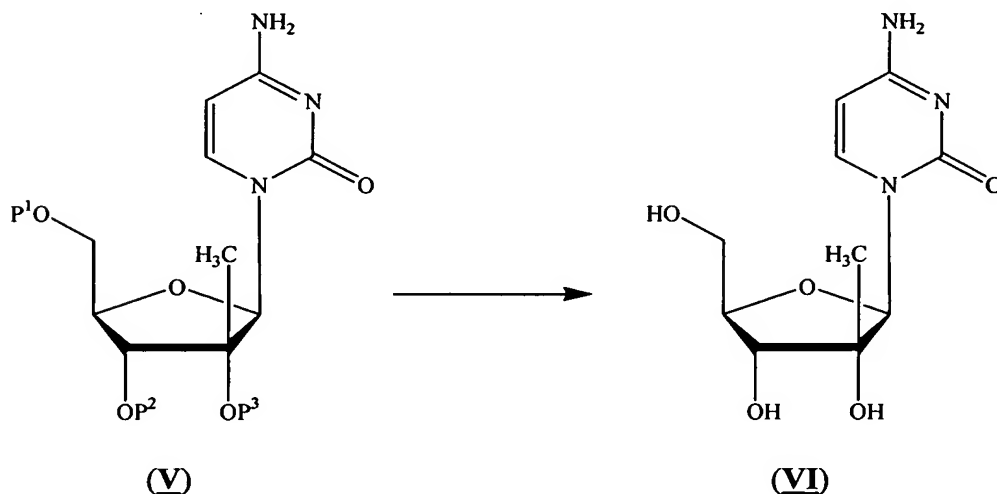
- (e) reacting the optionally protected 2-C-methyl- β -D-ribofuranose with cytosine and an activator, optionally in the presence of a Lewis acid, to form an optionally protected 2'-C-methylcytidine



wherein each P^1 , P^2 , P^3 , and P^4 is independently hydrogen or a suitable oxygen protecting group;

and then

- (f) optionally deprotecting the optionally protected 2'-C-methylcytidine to form optionally protected 2'-C-methylcytidine



if necessary.

77. The process of claim 76, wherein, each P¹, P², P³, and P⁴ is independently hydrogen or an acyl.
78. The process of claim 76, wherein, each P¹, P², P³, and P⁴ is independently hydrogen or a benzoyl.
79. The process of claim 76, wherein the activator is a silylating agent.
80. The process of claim 79, wherein the silylating agent is BSA, HMDS, TMSCl, or TBDPSCl.
81. The process of claim 79, wherein the silylating agent is BSA.
82. The process of claim 76, wherein the reaction of step (e) is accomplished with a Lewis acid selected from the group consisting of SnCl₄, BF₃, AlCl₃, TiCl₃, TiCl₄, FeCl₃, SnCl₂, and any mixture thereof.
83. The process of claim 82, wherein the Lewis acid is SnCl₄.
84. The process of claim 76, wherein the reducing agent is sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), optionally in a solvent.
85. The process of claim 84, wherein the solvent is ethanol.
86. The process of claim 76, wherein the process further comprises the steps of esterifying the 3'-position of the 2'-C-methyl-cytidine with an ester moiety.
87. The process of claim 86, wherein the ester moiety is an amino acid.
88. The process of claim 87, wherein the amino acid is L-valinyl.